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Real Benefit of Anthracycline-Based Chemotherapy in Elderly and Impaired Patients: a Retrospective Analysis

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Abstract

Non-Hodgkin Lymphoma (NHL) is a frequent cancer in elderly population. Comorbidities often influence the choice among different treatment options; particularly, concern about anthracyclines' cardiotoxicity induces to select less effective chemotherapy regimens. The present retrospective study includes NHL patients treated in a single institution with and without antracyclines; clinical results have been analysed comparing both elderly (> 70 years) and not-elderly and impaired and not impaired population.

68 patients affected by NHL, diagnosed between 1996 and 2011, have been included. Median OS of whole population was 34 months; there was no significative difference in OS related to age or comorbidities among patients treated with anthracyclines-based regimens. Median OS of elderly patients not treated with anthracyclines resulted significantly lower, irrespectively of comorbidities (20 months); 94% of elderly patients who undergone anthracyclines-based regimen reported symptoms relief and performance status improvement, compared to 75% of elderly not treated with anthracyclines.

Results of this retrospective analysis suggest that anthracyclines-based chemotherapy produces a significant improvement in OS and QoL,even in elderly or impaired patients. Comorbidities and age don't seem absolute contraindications to anthracycline-based chemotherapy.

Keywords: NHL; Cancer treatment; Comorbidity; Cardiotoxicity; Performance status; Quality of life

Introduction

Non-Hodgkin lymphoma is a common cancer in elderly patients [1]. In addition to classical prognostic factors, such as a poor performance status, elderly patients present with variable degrees of comorbidities and functional impairment, which account for a reduced tolerance of chemotherapy [2-4]. Although there are few prospective studies on treatment of elderly patients affected by NHL, retrospective analysis have shown that, in general, they have worse outcomes than younger patients, even if lymphoma in elderly is equally responsive to treatment [5-8].

Usually, the backbone of the first-line therapy of non-Hodgkin lymphomas is doxorubicin. Despite well-known cardiotoxicity of this drug [9], therapy guidelines are lacking in elderly, so that doxorubicin (DOX) use in these patients is a common concern in clinical practice, leading frequently to underpowered treatment [9]. However, some studies have suggested that not only an attenuated DOX-based regimen might be safely administrated to over 80 aged patients, but also a dose-dense DOX-based regimen might be tolerated by elderly patients with impaired cardiac function [10-12]. We wondered whether anthracyclines really determine a survival advantage in presence of comorbidities. A further, but not less important, question is the possible deterioration of quality of life (QoL) in these sometimes frail patients.

We present a retrospective study on NHL patients treated in a single institution with and without antracyclines, analysed in relation to age and presence of functional impairment. Impact of treatment on QoL was evaluated according to changes of performance status (PS) and frequency of side effects.

Patients and Methods

Patients selection

We performed a review of all the patients affected either by indolent or aggressive newly diagnosed NHL, who completed a course of treatment in our institution between 1996 and 2011. We included all the patients affected by a biopsy-proven NHL, irrespectively of good, intermediate or poor prognosis; they were classified according to the proper prognostic index and to Ann Arbor staging system [13-15]. Main exclusion criteria were concomitant malignant diseases (except prostatic carcinoma treated with radical surgery or radiotherapy) or absolute contraindications to any chemotherapy such as severe liver or renal disease. We included a total of sixty-eight patients (age range 26-79 years).

Patients subgroups were defined based on age (<70 versus >70 years), functional impairment (0-1 versus >1 systemic comorbidities) and inclusion of an anthracycline in the chemotherapy regimen. Patients receiving at least one dose of doxorubicin were included in the anthracycline treatment group [16].

Treatment

According to cardiac impairment, age or histologic subtype, patients were treated with R-CHOP q3w (rituximab 375 mg/sqm i.v., day 1; cyclophosphamide 750 mg/sqm i.v., day 2; vincristine 1.4 mg/sqm i.v., day 2; doxorubicin or unpegilated liposomal doxorubicin

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50 mg/sqm i.v., day 2; prednisone 100 mg p.o. daily, day 2-6) or R-CVP (rituximab 375 mg/sqm i.v., day 1; cyclophosphamide 750 mg/sqm i.v., day 2; vincristine 1.4 mg/sqm i.v., day 2; prednisone 100 mg p.o. daily, day 2-6) regimen [17,18]. Treatment was continued for 6 cycles or a maximum of 8 cycles. Maintenance rituximab was started within 6 months from the last dose of induction therapy in responding patients with an indolent histologic subtype and was carried out every 3 months for a maximum of 2 years (8 doses in total) in absence of unacceptable toxicity or disease progression [19]. SHT3 antagonists as antiemetic therapy and allopurinol for preventing hyperuricemia from tumour lysis syndrome were always given. In case of neutropenia or thrombocytopenia, subsequent cycle was delayed by one week until neutrophil and/or platelet count reached 1.0×10^9/L or 90×10^9/L, respectively. Granulocyte-stimulating factors (G-CSF) and erythropoietin were administered subcutaneously either as secondary prophylaxis or as treatment of, respectively, chemotherapy-induced neutropenia (Neu < 0.5×10^9/L) or anaemia (with <10 g/L haemoglobin concentration).

Basal assessment before the first treatment cycle consisted of full history, physical examination, thoracic and abdominal computerised scan, echocardiogram and bone marrow biopsy. Laboratory analyses included lactate dehydrogenase, beta2-microglobulin, serum creatinine, transaminase, bilirubin, alkaline phosphatase, serum electrophoresis and complete blood cell; in addition, Epstein-Barr, hepatitis B and C virus serology was evaluated before treatment. Tumour measurements were performed by clinicians and local radiologists.

Measurements of efficacy

Response was determined after 4 cycles and at the end of treatment with thoracic and abdominal scan. In this retrospective series, ^{18}FDG-positron emission tomography was not mandatory for assessment of response. Biopsy of bone marrow was required for confirming response when marrow was involved at baseline. Complete remission was defined as the disappearance of all clinical disease; partial remission was defined as at least 50% reduction of all disease manifestations. Response was measured according to revised criteria for malignant lymphoma [20].

Overall survival (OS) was calculated from the first day of chemotherapy until death by any cause; progression-free survival was calculated from onset of chemotherapy until progression of disease or death by any cause. Questionnaires on quality of life were not planned at time of treatment so the impact of therapy on general health status was derived from Performance Status (ECOG) before and at the end of treatment and from evaluation of adverse events and chemotherapy-related side effects.

Statistical methods

Due to the retrospective nature of the study, no *a priori* hypothesis was formulated and no sample calculation based on power consideration was carried out. All the analyses are regarded as exploratory and descriptive. In general, comparisons of subgroups in relation to time-to-event data were carried out using the Chi-square method. The product limit method (Kaplan-Meier estimates) was used for estimation of medians in relation to time-to-event variables. Best overall response rate and disease control rate were analyzed by Cochran-Mantel-Haenszel (CMH). Patients were stratified by age, comorbidities and anthracyclines-based regimen.

Safety analyses were performed on all population. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 and summarized according to worst grade per patient according to the National Cancer Institute – Common Toxicity Criteria (version 3.0).

Results

Sixty-eight patients affected by indolent (16%) or non-indolent (84%) NHL, treated between 1996 and 2011, were included in this retrospective study. Characteristics of the entire patients' population are summarized in Table 1. Sixteen patients were between 70 and 75 years (24%) and 9 patients (13%) were older than 75 years; taken together, they represent the population defined as "elderly" in the present study. Twenty-two patients (32%) had a poor prognosis according to the proper prognostic index; fifty-seven (84%) had B symptoms. Cardiovascular risk factors were present in 33 (53%) patients: 15 (19%) had cardiac comorbidities (either ischemic or arrhythmic cardiac disease), 23 (35%) had hypertension and 12 (18%) diabetes mellitus, both under active treatment.

Seventeen patients (68%) in elderly group underwent anthracycline-based therapy. Only seven of these patients were treated with liposomal doxorubicin; due to small size of the sample, a descriptive comparison was not possible.

Median OS of the entire population of patients was 34 months. In patients treated with anthracycline-based combination therapy median OS was 130 months, without any difference among older (>70 years) and younger patients, whereas it was significantly lower (p=0.047; HR 0.29, 95%CI 0.08-1.08) in those who received a chemotherapy non containing anthracycline (20 months – Figure 1). Similarly, median OS was 140 months in impaired patients who received anthracycline-based therapy, independently of age; the median OS was significantly lower (20 months – p=0.007; HR 0.25 95%CI 0.04-1.45) in impaired patients not treated with anthracycline-based chemotherapy (Figure 2).

Most patients had an improvement of PS after chemotherapy; respectively thirty-nine out of forty-three younger (91%) and twenty-two of twenty-five elderly patients (88%) (Figure 3). Sixteen (94%) out of seventeen elderly patients submitted to anthracyclines' combination therapy experienced symptoms relief and improvement of PS (ECOG); a similar percentage was reached in <70 years old patients (91%). In the smaller group of elderly patients not treated with anthracyclines, fewer patients experienced symptoms improvement (75%) (Figure

PATIENTS' CHARACTERISTICS	N° (%)
Patients included	68
Median age at diagnosis	52 range 26–79
<70	43/68 (63)
70-75	16/68 (24)
>75	9/68 (13)
Male gender	37/68 (54)
Indolent LNH	11/68 (16)
Non-indolent LNH	57/68 (84)
Good prognosis	15/68 (22)
Intermediate prognosis	31/68 (46)
Poor prognosis	22/68 (32)
Comorbidities ≥ 2	39/68 (57)
Cardiovascular risk	36/68 (53)
Hypertension	24/68 (35)
Cardiac risk	13/68 (19)
Diabetes	12/68 (18)

Table 1: Patients' charateristics.

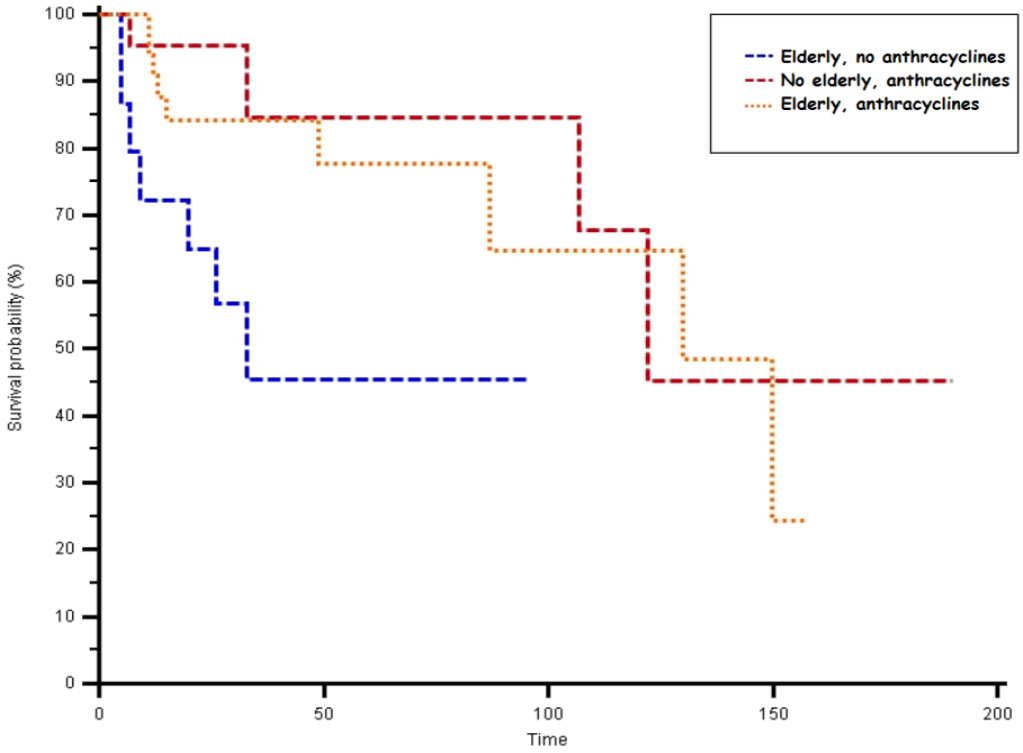

Figure 1: Patients treated with chemotherapy non containing anthracycline.

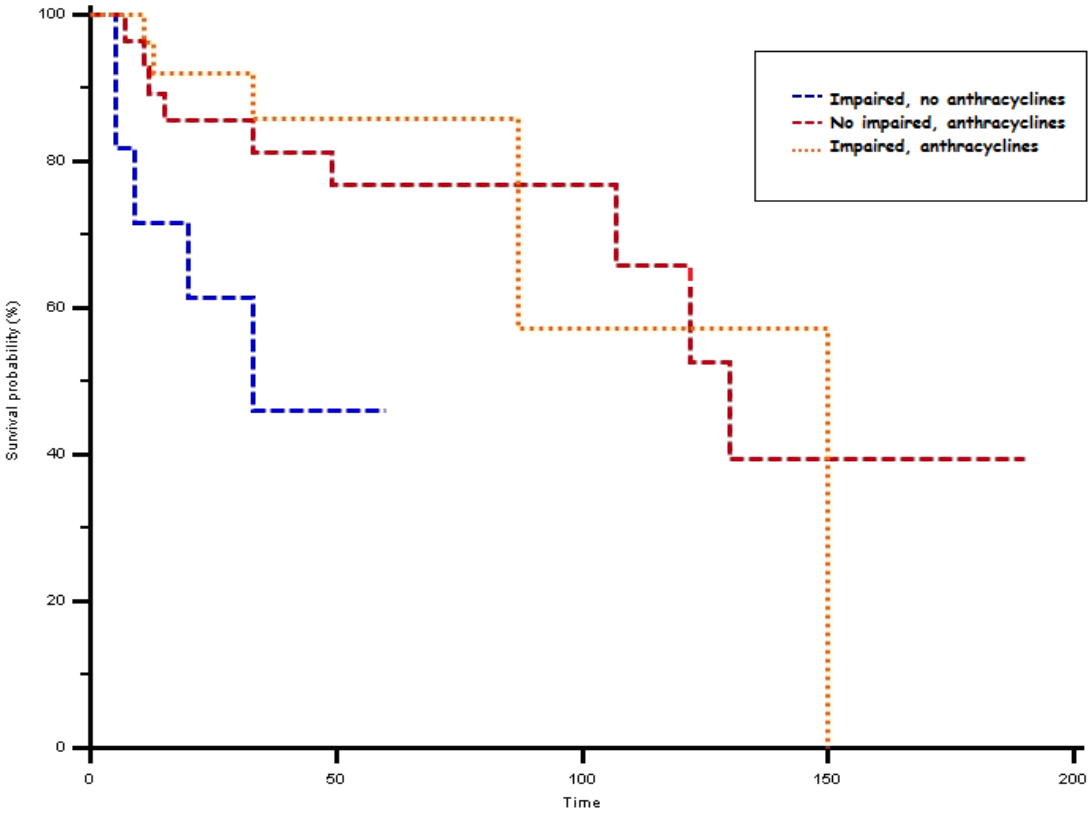

Figure 2: In impaired patients not treated with anthracycline-based chemotherapy.

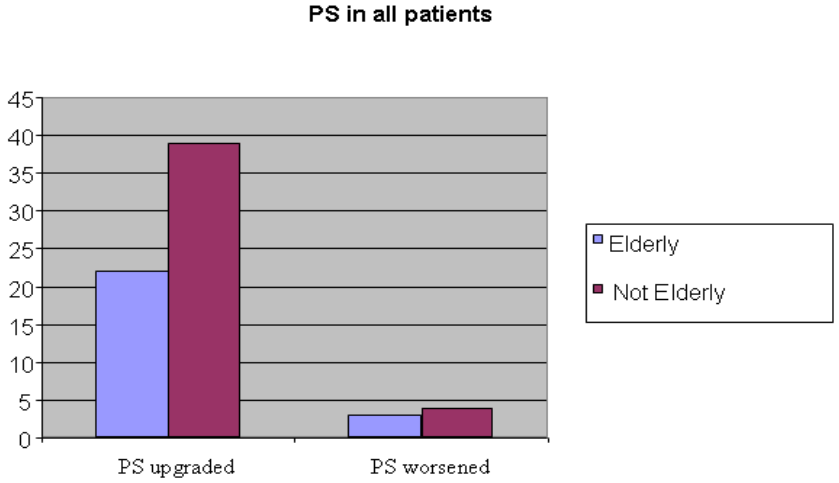

Figure 3: PS in all patients.

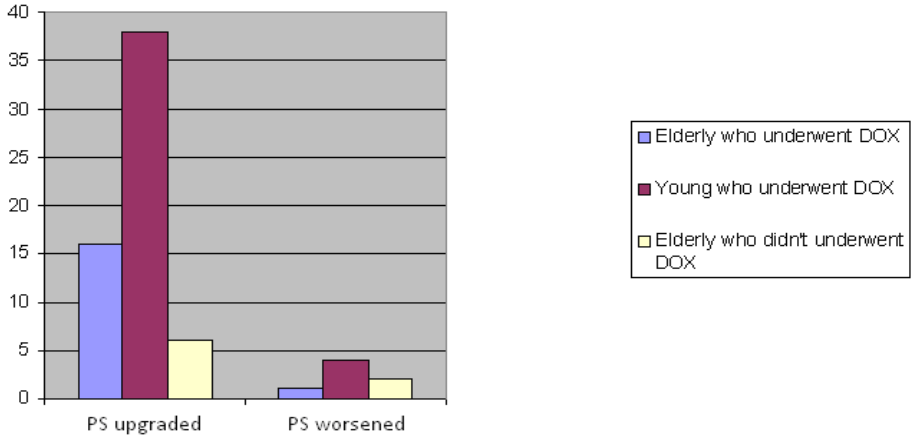

Figure 4: PS in respect to age and doxorubicin.

4). Overall, thirty-nine patients (57%), nineteen of whom aged more than 70 years (28% of the whole sample) experienced a grade 3/4 toxicity, mainly haematological. Among these patients 20/45 (44.4%) and 19/23 (82%) – respectively younger and elderly - needed dose reduction or interruption of therapy. Only one serious cardiologic event (paroxysmal atrial fibrillation) was observed in an elderly patient treated with CVP; this did not prevent the conclusion of therapeutic program after recovery from the acute event.

Discussion

In the last decades the progressive increase of average age in western countries has faced oncologists with the need of looking after a large population of elderly patients. Effects of exposure to chemotherapy in these patients are often unpredictable, due to the possibility both of different efficacy and poor tolerance in relation to metabolic impairment as well as to frequent comorbidities. Very few trials in oncology have been devoted to or have included a significant percentage of elderly patients, so evidence-based recommendations are scarce. Therefore, treatment strategy of such patients is often based on clinical evaluation of their general status and this approach has been also included in 2012 ESMO Guidelines on DLBCL, which suggest treating elderly patients according to their general health status as a result of combining comorbidities and aging [21]. Despite a number of studies have included elderly patients and one of these has enrolled only patients aged between 61 and 69 years, data remain few in particular whether >70 year old patients are considered [17, 21-27]. This really old population is more often prone to comorbidities as well as to frailty and it is clinically more challenging because the chance of cure with chemotherapy might be frustrated by excess of life-threatening adverse events. The potential of combining more harmful effects of treatment and more difficult recovery attracts a particular attention on QoL and PS. However, it seems that elderly patients can tolerate also dose-intensified regimens [23], and, with those regimens, age is not predictive of survival benefit [24]. In the same way, Rituximab maintains its additive value (in terms of PFS) both in elderly and in young patients [25].

In our retrospective study we have considered “elderly” only 70-year or older patients and we have attempted to evaluate feasibility,

efficacy and tolerability of doxorubicin in this population. Despite small-sized sample, the impact of doxorubicin on OS seems very impressive in all subgroups of patients, including those elderly and functionally impaired. This finding is noteworthy considering that OS in elderly patients is related to lymphoma remission as well as to comorbidities and functional impairment. In addition, the vast majority of our patients (94%) experienced symptoms relief and improvement of PS after treatment, apart from age and functional impairment. Out of three elderly patients reporting a worsening of symptoms and PS, only one was having doxorubicin. Furthermore, decrease of ejection fraction in elderly was moderate and similar to that observed in younger patients. Only one of our elderly patients experienced a G3 cardiologic adverse event, which does not seem to have significantly influenced clinical outcome.

Our findings are in line with two recent retrospective analyses. While analysing the effects of a reduced dose intensity in a large elderly cohort, Eyre et al. [28] found that patients aged 70-80 who were planned to receive full-dose chemotherapy had improved PFS compared to those with planned treatment-attenuation; moreover, fit patients of the same age could tolerate full dose R-CHOP with excellent outcomes, while patients aged more than 80 years could obtain long-term PFS with R-miniCHOP. This is consistent with the results of both the study from Peyrade et al. (10) and the retrospective analysis from Ha et al. [29], which demonstrated that in elderly patients both PFS and OS change significantly according to doxorubicin dose intensity. A different study [30] seems to contradict these results, as doxorubicin was not significantly associated to mortality; however, this last study only examined patients aged over 80 years, and a OS improvement with lower doses of anthracyclines was reported.

Taken together, these results consistently suggest that an optimal treatment of lymphoma, including doxorubicin, results in a clear improvement both of OS and QoL – at least for patients aged 70-79 years. In other terms, symptoms mainly depend on lymphoma, even in elderly and/or impaired patients, and a better control of neoplastic disease leads to increased survival and to overall decrease of symptoms.

Major limits of this retrospective study are small-sized sample and lack of formal questionnaries on QoL; speculations on this last aspect are surrogated by PS and symptoms. Moreover, our sample does not include any patient aged 80 years or more. However, as a matter of fact, effects on survival and symptoms control in our study are so large that seems difficult to think that they depend on chance; our results are also consistent with the known literature. Therefore, we can reasonably conclude that anthracyclines may be safely used and that they are associated with better outcome in terms of survival and symptoms control, even in elderly patients.

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